The Interface

TRAMADOL:

Seizures, Serotonin Syndrome, and Coadministered Antidepressants

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This ongoing column is dedicated to the challenging clinical interface between psychiatry and primary care—two fields that are inexorably linked.

ABSTRACT

Tramadol (Ultram®) is a commonly prescribed analgesic because of its relatively lower risk of addiction and better safety profile in comparison with other opiates. However, two significant adverse reactions are known to potentially occur with tramadol—seizures and serotonin syndrome. These two adverse reactions may develop during tramadol monotherapy, but appear much more likely to emerge during misuse/overdose as well as with the coadministration of other drugs, particularly antidepressants. In this article, we review the data relating to tramadol, seizures, and serotonin syndrome. This pharmacologic intersection is of clear relevance to both psychiatrists and primary care clinicians.

KEY WORDS

tramadol, analgesic, opiate, seizure, serotonin syndrome, antidepressant, polypharmacy, psychiatrist-physician interface

INTRODUCTION

According to Miller et al,[1] chronic pain affects a vast number of US patients and results in billions of dollars in annual healthcare expenditures. In Australia, the cost of managing chronic pain is estimated to be $34 billion per year.[2] Given the narcotic alternatives for treatment, tramadol (Ultram®) is a unique pharmacological bullet in the fight against chronic pain. To attest to its popularity, prescriptions for tramadol in Canada reached almost 26 million in 2006, representing total sales of $800 million.[3] In this edition of The Interface, we discuss two potential adverse events related to this commonly prescribed analgesic—seizures and serotonin syndrome.

DESCRIPTION OF TRAMADOL

Tramadol is an analgesic medication that is a synthetic analogue of codeine. In comparison with other opiates, tramadol is renowned for having less abuse potential and less respiratory depression.[4] In terms of specific neurotransmitter effects, at the central level, tramadol is a mu-opioid receptor agonist. The affinity of tramadol for mu-opioid receptors (analgesic effect) is 10-fold less than codeine. However, the active metabolite of tramadol, o-desmethyltramadol, has a far greater affinity (up to 200-fold) than the parent compound. In addition to its central effects on mu receptors, at

TABLE 1. Potential severity of drug interactions with tramadol according to *Clinical Psychopharmacology*[4]

Severe (contraindicated/not usually taken concurrently)
Monoamine oxidase inhibitors
Selegiline transdermal
Major (may result in potential deterioration—patient should be monitored)
Bupropion
Duloxetine
Nefazodone
Selective serotonin reuptake inhibitors
Venlafaxine
Moderate (bothersome or unnoticeable—limited clinical effects)
Maprotiline
Mirtazapine
Tricyclic antidepressants
St. John's Wort

the peripheral level, tramadol inhibits serotonin and norepinephrine reuptake. These latter effects are likely to be an important element in analgesia, but may also account for some of the adverse properties of the drug.[4]

According to Reeves and Cox,[5] tramadol has many characteristics that are similar to venlafaxine, including structural similarities and serotonergic/noradrenergic reuptake inhibition. In keeping with this perspective, Yalcin et al[6] describe tramadol as having antidepressant-like effects. Not surprisingly, using liquid chromatography to detect levels of tramadol in urine, venlafaxine may cause false positive results.[7]

DRUG INTERACTIONS

Tramadol accounts for a significant number of drug interactions. For example, in an Australian veterans study, Roughead et al[8] examined adverse drug interactions in 46,859 participants taking antidepressants. Of the 8.1 percent who experienced these interactions, tramadol was the most often implicated drug (3.6%).

Of these various interactions, tramadol has the potential to trigger two dramatic events—seizures and serotonin syndrome. These may develop during tramadol monotherapy either at routine or excessive doses, but are particularly likely during tramadol coadministration with antidepressants (Tables 1 and 2).[4,9] (In addition to antidepressants, tramadol may interact with a number of other psychotropic drugs including antipsychotics and anticonvulsants.)

TRAMADOL AND SEIZURES

Tramadol monotherapy. Seizures have been reported with tramadol monotherapy in animal and human studies,[4] both at recommended[10] and high doses.[11] With regard to appropriately prescribed doses, Gardner et al[12] examined a cohort of more than 9,000 patients taking tramadol in a managed care population. While fewer than one percent (80) had an alleged seizure after their first prescription of tramadol, the risk increased 2- to 6-fold when adjusted for selected medical comorbidities and concomitant prescribed drugs. In an Australian study, Labate et al[13] found that 8.2 percent of new-onset seizures were accounted for by tramadol exposure. They state that, "In our First Seizure Clinic, tramadol [was] the most frequently suspected cause of provoked seizures." However, one additional study found no increased risk of seizures with tramadol monotherapy,[14] and another concluded that there was no higher risk compared to other analgesic monotherapies.[15]

Tramadol abuse/overdose. With regard to abuse and/or overdose, tramadol's neurotoxicity is speculated to be related to the reuptake inhibition of serotonin and norepinephrine, rather than its opioid effects.[16] Patients with an existing seizure disorder appear to be most at risk for adverse effects. To illustrate the risk of excessive dosing, in a study of tramadol abusers, Jovanovic-Cupic et al[17] found that 54.4 percent of the sample reported at least one tonic/clonic seizure during the three-year study period.

With regard to seizures in genuine overdoses, Thundiyil et al[18] examined all such cases logged by the California Poison Control System in 2003. Of the 386 identified cases of seizures with drug overdoses, tramadol accounted for 29 (7.5%). Likewise, Spiller et al[16] examined 126 tramadol overdoses that were documented by seven poison control centers and found that eight percent of the victims experienced brief seizures.

Tramadol and antidepressants. The coadministration of antidepressants with tramadol appears to heighten the risk for seizures. When Boyd examined 83 cases of tramadol-associated seizures, he found that nearly half occurred in the presence of other prescribed drugs; more than 50 percent of these coadministered

drugs were antidepressants (i.e., selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], venlafaxine, bupropion).[19] Therefore, in individuals taking tramadol, concomitant treatment with antidepressants, especially TCAs or SSRIs, should be undertaken with caution.[20]

The "Dear Healthcare Professional" letter. In response to clinical concerns about the risk of seizures with tramadol, a "Dear Health Professional" letter was distributed by the manufacturer to prescribers in 1996, advising that, up to that time, "…83 domestic reports of an adverse event described as seizures or convulsions…" had been reported.[21] In this letter, the manufacturers noted that the risk of seizures with tramadol was heightened in individuals taking TCAs or SSRIs.

In the aftermath of this letter, Shatin et al[22] examined changes in prescriber patterns. Prior to the letter, 22.2 percent of managed care members received an antidepressant within 30 days of their initial prescription for tramadol. After the letter, 19 percent received an antidepressant within 30 days of their initial prescription for tramadol—a small and insignificant change in response to the manufacturer's warning.

TRAMADOL AND SEROTONIN SYNDROME

Serotonin syndrome (SS). SS is a potentially lethal event that is caused by excessive serotonergic agonism of serotonin receptors in the central and peripheral nervous system. SS may develop as a result of increased serotonin synthesis, decreased serotonin metabolism, increased serotonin release, inhibition of serotonin reuptake (e.g., SSRIs), and/or direct agonism of serotonin receptors. The syndrome is most often the result of a prescription drug, overdose of causative drugs, and/or complex interactions among several drugs. Three key clinical features of this syndrome are as follows: (1) neuromuscular hyperactivity (e.g., tremor, clonus, myoclonus, hyperreflexia, rigidity); (2) autonomic hyperactivity (e.g., diaphoresis, fever, tachycardia, tachypnea); and (3) altered mental status (e.g., agitation, confusion).[23] There is no designated laboratory study for the diagnosis of SS.[24] Management consists of discontinuing the offending agent and providing supportive care. Signs and symptoms typically resolve within 24 hours after the discontinuation of the causative medication, except in patients exposed to drugs with long elimination half-lives.[25] Serotonin antagonists, such as cyproheptadine, may help alleviate symptoms, although the efficacy of this pharmacological intervention has not been rigorously studied.[25]

Tramadol as a factor. Like the risk of seizures, SS may occur with tramadol monotherapy but appears to be more common following either excessive use/overdose or with the coadministration of other medications, particularly antidepressants. With regard to the antidepressant interactions, SS has been reported with combinations of tramadol and the following: fluoxetine,[26–28] sertraline,[29–31] paroxetine,[32–35] citalopram,[36] fluvoxamine,[37] venlafaxine,[38,39] and TCAs.[40] In addition, Gnanadesigan et al[41] reported four cases of SS among residents in a long-term care facility, all who were prescribed tramadol in combination with either SSRIs or mirtazapine. The majority of these preceding case reports describe elderly individuals who were oftentimes prescribed other medications as well.

TABLE 2. Potential drug interactions with tramadol according to *AccessMedicine*[9]

MAO Inhibitors Tramadol may enhance the neuroexcitatory/seizure-potentiating effect of MAO Inhibitors. *Risk D: Consider therapy modification*
Selective Serotonin Reuptake Inhibitors SSRIs may enhance the neuroexcitatory/seizure-potentiating effect of tramadol and enhance the serotonergic effect of selective serotonin reuptake inhibitors, causing serotonin syndrome. *Risk D: Consider therapy modification*
Tricyclic Antidepressants TCAs may enhance the neuroexcitatory/seizure-potentiating effect of tramadol. *Risk C: Monitor therapy*

CONCLUSIONS

In primary care settings, tramadol is a commonly prescribed synthetic analgesic. Two potential adverse reactions of tramadol are seizures and SS. Either of these reactions may occur with tramadol monotherapy, but both appear to be much more common with either abuse/overdose or in combination with other drugs, particularly antidepressants. These adverse reactions appear to be more common in the elderly. The majority of commonly prescribed antidepressants have been implicated in both of these adverse reactions.

Clinicians are advised to be mindful of these potential adverse sequelae when prescribing antidepressants to patients on tramadol, particularly in the elderly and/or those who might be at a heightened risk (i.e., individuals with epilepsy, head injuries, neurological dysfunction). If coadministration is undertaken, we advise careful monitoring for these two particular hazards. Tramadol is a remarkable drug, but like all drugs, effective use entails balancing the benefits versus the risks.

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